No. 17-1480

IN THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

AMGEN INC.; AMGEN MANUFACTURING, LIMITED; AND AMGEN USA, INC.,

Plaintiffs-Appellees

v.

SANOFI; SANOFI-AVENTIS U.S. LLC; AVENTISUB LLC, F/D/B/A AVENTIS PHARMACEUTICALS INC.; AND REGENERON PHARMACEUTICALS, INC.,

Defendants-Appellants

On Appeal from the United States District Court
for the District of Delaware
No. 14-CV-1317-SLR

AMGEN'S OPPOSITION TO DEFENDANTS-APPELLANTS' EMERGENCY MOTION FOR STAY PENDING APPEAL AND EXPEDITED BRIEFING

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CERTIFICATE OF INTEREST

Counsel for Plaintiffs-Appellees Amgen Inc.; Amgen Manufacturing, Limited; and Amgen USA, Inc. certifies the following:

1. The full names of the parties represented by me are Amgen Inc.; Amgen Manufacturing, Limited; and Amgen USA, Inc.

2. The names of the real parties in interest are Amgen Inc.; Amgen Manufacturing, Limited; and Amgen USA, Inc.

3. Amgen Inc. owns 10 percent or more of the stock of Amgen Manufacturing, Limited and Amgen USA, Inc. No publicly held company owns 10 percent or more of Amgen Inc.

4. The names of all firms and the partners or associates that appeared for the parties now represented by me in the trial court or are expected to appear in this Court (and who have not or will not enter an appearance in this case) are:

AMGEN INC.: Stuart L. Watt; Wendy A. Whiteford; Erica S. Olson; Dennis J. Smith; Emily C. Johnson; Steven Tang

YOUNG CONAWAY STARGATT & TAYLOR: Melanie K. Sharp; James L. Higgins

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January 27, 2017

/s/ Daryl L. Joseffer
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C	Official Transcript of jury trial held on March 9, 2016
D	Transcript of Hearing held on March 23, 2016 [REDACTED]
E	Official Transcript of jury trial held on March 10, 2016
F	Official Transcript of jury trial held on March 11, 2016
G	Final Jury Instructions
H	Memorandum Opinion (denial of Defendants' motions for JMOL and new trial)
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J	Memorandum Order granting in part and denying in part Amgen's *Daubert* motion
K	Official Transcript of pretrial conference held on February 22, 2016
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R	Curriculum Vitae of Dr. Evan A. Stein
S	Prescribing Information (Repatha)
T	Prescribing Information (Praluent)

Ex.	Description of Exhibit
U	2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults
V	FDA Advisory Committee Briefing Document Praulent (alirocumab), June 9, 2015
W	Cannon et al, *Relationship Between Major Adverse Cardiovascular Events and Achieved Low Density Lipoprotein Cholesterol Levels in Phase 3 Odyssey Trials of Alirocumab versus Control*, PRESENTATION NO. 913-04 (April 4, 2016)
X	Ray et al, *Relationship Between Percentage Reduction in Low-Density Lipoprotein Cholesterol Levels and Major Atherosclerotic Cardiovascular Disease among Patients Treated with Statins +/- Alirocumab or Ezetimibe in the Phase 3 Odyssey Trials*, JACC, 67:13, PRESENTATION NO. 1124M-05 (2016)
Y	Ray, K. K., et al., *Reductions in Atherogenic Lipids and Major Cardiovascular Events: A Pooled Analysis of 10 ODYSSEY Trials Comparing Alirocumab With Control*, Circulation, 134:1931-1943 (2016)
Z	Ito et al, *PCSK9 Inhibition With Monoclonal Antibodies: Modern Management of Hypercholesterolemia*, J. Clin Pharmacol., 57(1):7-32 (June 21, 2016)
AA	Nicholls, S. J., et al., *Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients: The GLAGOV Randomized Clinical Trial*, JAMA, 316(22):2373-2384 (2016)
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Ex.	Description of Exhibit
FF	Praluent Safety Information
GG	Morgan Stanley, Deep Dive on the PCSK9s: Praluent and Repatha, 11/20/2016
HH	Morgan Stanley Tr.
II	Regeneron Tr.
JJ	JTX 266
KK	"Regeneron CEO: Amgen not putting patients first," *PharmaLive*, Jan. 9, 2017, http://www.pharmalive.com/regeneron-ceo-says-amgen-not-putting-patients-first-in-patent-dispute/
LL	"A Stakeholder meeting on ensuring patient access to affordable drug therapies", National Academies of Sciences – Engineering – Medicine, January 23, 2017
MM	CVS, "CVS Health Announces Formulary and Therapy Strategy for PCSK9 Inhibitors," news release, Nov. 23, 2015, quote from Troyen A. Brennan, MD, MPH, executive vice president and Chief Medical Officer, CVS Health
NN	Stein Decl.
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PP	Berndt Decl.

INTRODUCTION

Defendants are admitted infringers who rushed to market during the course of this litigation. Their product works in the same way to treat the same patients as Amgen's Repatha. The district court properly granted the injunction and refused to stay it. With the trial record so strongly supporting the validity verdict and the court's judgment, and with Repatha being able to meet the needs of all patients, this Court should also deny Defendants' stay request.

In arguing for a stay, Defendants resort to hyperbole, misstatements, reliance on self-inflicted injuries, and scare tactics regarding the "public interest." The only "shocking" thing that happened during trial was Defendants' decision to launch their Praluent product at risk, after agreeing to an expedited pre-trial schedule in lieu of preliminary-injunction proceedings, and with a jury trial less than eight months away. Defendants stipulated to infringement and had a full and fair opportunity to prove their invalidity case. Both the jury and the court rejected them. It is time Defendants stop infringing.

None of this comes as a surprise. Defendants knew that Amgen was the innovator here, and early on, with Amgen's published patent application in hand, recognized that there would be "patent issues." Amgen filed first for product approval with the FDA. Defendants' response was to pay $67.5 million to purchase a third-party priority-review voucher, which allowed them to leapfrog Amgen in the FDA approval queue. As a result, Defendants were the first to obtain FDA approval and to launch their product, betting that the court would not enjoin them. That decision is the cause of every harm Defendants cite. Countenancing Defendants' launch-at-risk-don't-take-us-off-the-market strategy by granting a stay will open the door to such irresponsible actions in all pharmaceutical cases and gut innovation in the biopharmaceutical industry.

No patient will go untreated or be harmed by removing Praluent from the market. As described in detail below and in the accompanying declarations, Repatha is FDA approved to safely and effectively treat every indication and every patient for whom Praluent is approved. Both products are PCSK9 antibodies. Both bind to the same "sweet spot" and work by the same mechanism in the body to lower "bad"

cholesterol ("LDL-C"). As shown at trial, Amgen invested to manufacture and supply the entire market for PCSK9 antibodies and will appropriately support the transition of Praluent patients to Repatha.

Defendants are demonstrably wrong in relying on their "half-dose" option to assert that "thousands" of patients will be left without treatment options. Defendants ran this same argument below—conjuring an unsubstantiated safety concern about reducing LDL-C *too* much, to justify their half-dose Praluent option. The court properly rejected it, saying it would not substitute its judgment for the FDA's. Defendants even admitted there was "no evidence" of any such safety risk.

Defendants wrongly assert that a stay would preserve the "status quo." Defendants are continuing to compete on price to expand their market position and take more customers from Amgen. Defendants continue to bid on contracts covering 2018 and 2019, extending Amgen's irreparable injury further into the future. A stay would not preserve the status quo, unless by that Defendants mean that they will continue to cause harm to Amgen and trample on Amgen's patent rights.

Defendants argue for a stay because, in their view, the "many dubious rulings" of the district court make it "highly unlikely" that the judgment and the injunction ruling will "survive on appeal." But nothing in the court's rulings or the jury verdict provides any basis for reversing the judgment or injunction. The court thoughtfully and correctly applied basic rules of patent law as provided by statute and this Court's decisions. In granting JMOL on Defendants' obviousness defense, the court found Defendants' efforts insufficient to establish references as prior art. The court exercised its discretion to exclude post-priority-date evidence from both sides on the §112 defenses, finding such evidence confusing to the jury and at best cumulative. The court's "well characterized antigen" jury instruction was taken directly from this Court's decisions. And overwhelming evidence supported the jury's verdict.

Defendants' loudest complaints are directed at the court's injunction decision and the "public interest" factor, asserting that factor should be determinative. Although the court found that the public has an interest in "choice," the court balanced the equitable factors and, using its discretion, entered the injunction. On these facts and the

findings of the court, an injunction is the only appropriate remedy and should not be stayed.

ARGUMENT

Defendants' arguments for a stay here just repeat those made below in arguing against the injunction, are wholly speculative, and run counter to the facts presented at trial. Defendants cannot meet their burden of establishing entitlement to a stay under the traditional stay factors. Simply asserting self-inflicted injuries is not enough, as a stay "is not a matter of right, even if irreparable injury might otherwise result." *Nken v. Holder*, 556 U.S. 418, 433 (2009).

Defendants' contention that this Court "regularly" stays permanent injunctions is overblown. The Court has stayed some injunctions and denied stays of others. *See Mytee Prods. v. Harris Research*, 398 F. App'x 590 (Fed. Cir. 2010); *iLight Techs. v. Fallon Luminous Prods. Corp.*, 2009 WL 1939187 (Fed. Cir. July 1, 2009); *Celsis In Vitro v. CellzDirect*, 404 F. App'x 481, 482 (Fed. Cir. 2010). For the reasons explained below, the Court should deny a stay in this case.

A. Defendants Are Unlikely To Succeed On Appeal.

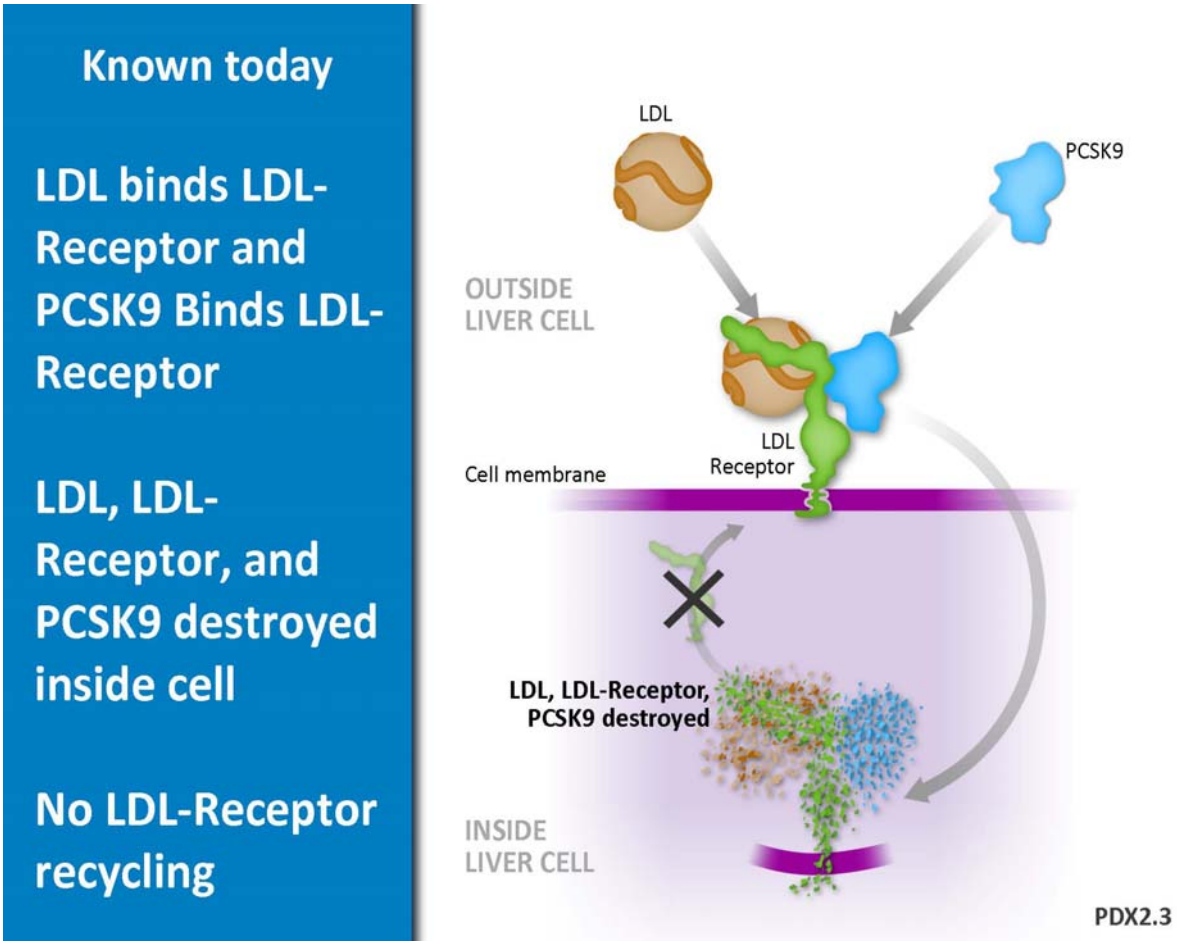
Given the substantial trial record and the findings of the district court, Defendants cannot show that they are likely to succeed on their appeal of the patent or injunction issues. On invalidity, Defendants bear the burden of showing that there was no substantial evidence supporting the jury's verdict that Defendants had failed to prove invalidity by clear and convincing evidence. *See L&W v. Shertech*, 471 F.3d 1311, 1320 (Fed. Cir. 2006). Defendants' challenges to the district court's exclusion of evidence and entry of an injunction are reviewed for an abuse of discretion. *See Siemens Med. Sols. USA v. Saint-Gobain Ceramics & Plastics,* 637 F.3d 1269, 1284 (Fed. Cir. 2011).

1. Background On The Invention.

Amgen was the first to invent monoclonal antibodies to a protein called PCSK9 that have the ability to dramatically lower LDL-C in patients. Amgen's PCSK9 antibodies have the potential to revolutionize the standard of care for treating heart disease—the leading cause of death in the U.S. Ex.OO¶6; *see also* Ex.NN¶35.

In the body, the LDL receptor ("LDLR") sits on the surface of liver cells and clears circulating LDL from the bloodstream. The LDL-LDLR complex enters into liver cells where the LDL is destroyed and the

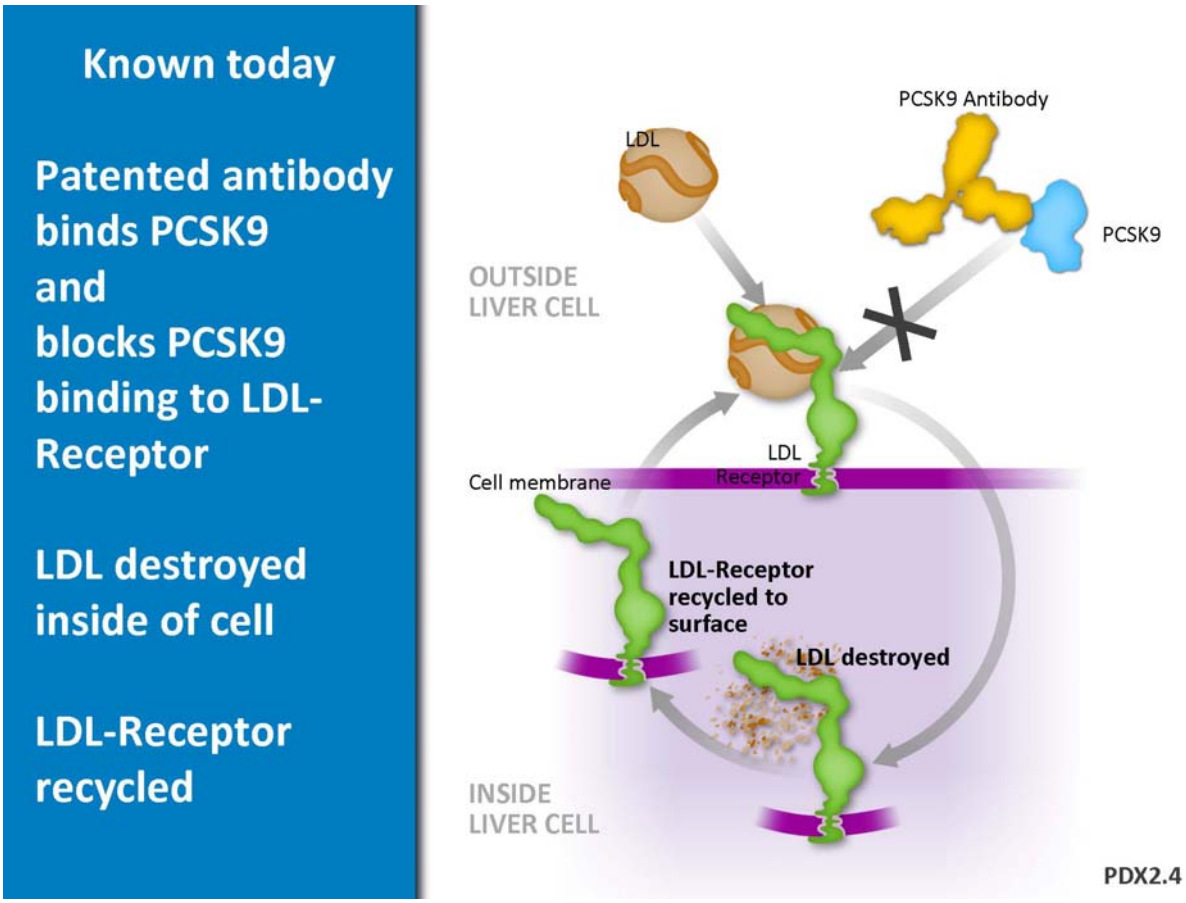
LDLR returns to the cell surface to capture more LDL. PCSK9 can bind to LDLR, and when it does the LDL-LDLR-PCSK9 complex is destroyed inside liver cells:



Ex.C,242:22-244:16; Ex.NN¶42.

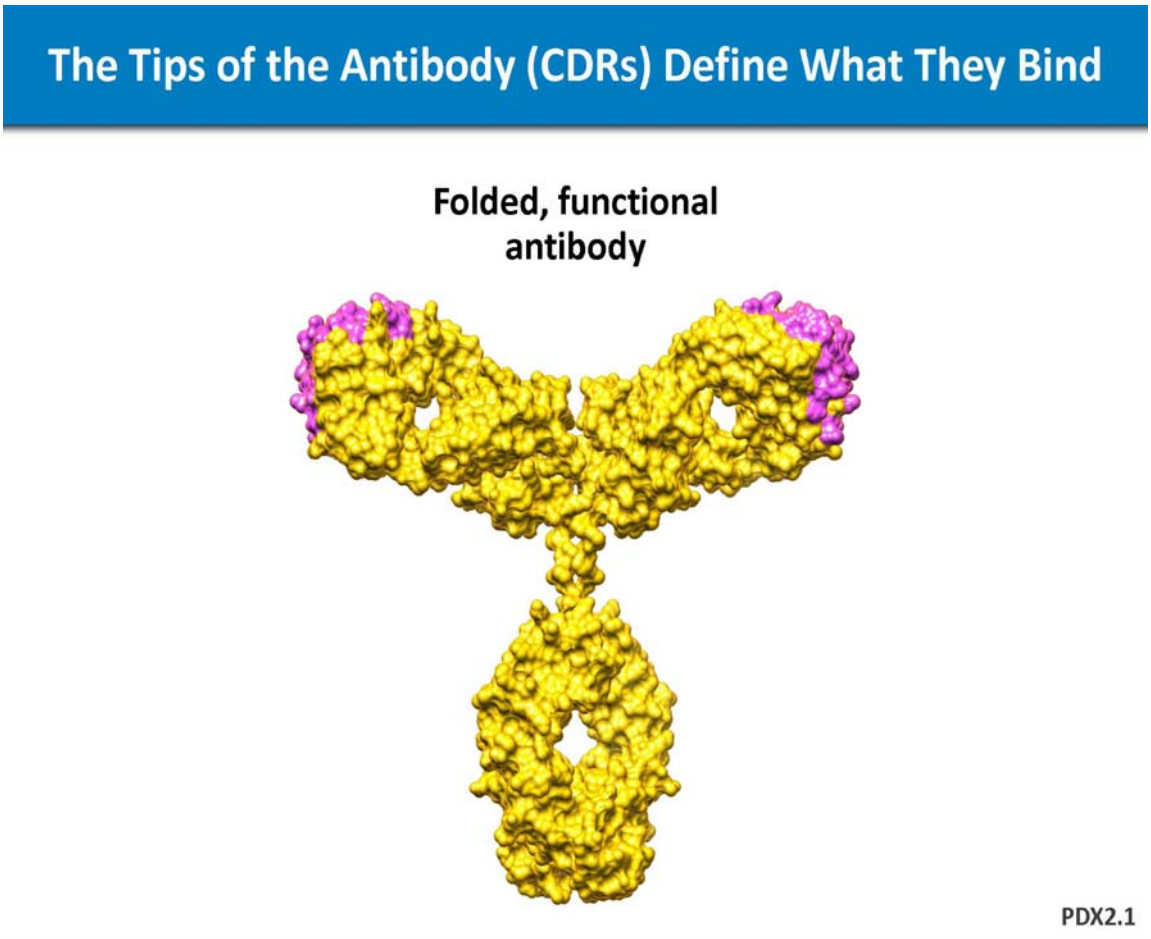
After several years of research efforts, Amgen invented antibodies that bind to PCSK9 and block the interaction of PCSK9 with LDLR, thereby protecting the LDLR from destruction and allowing it to recycle

to the cell surface and remove more LDL from the bloodstream:

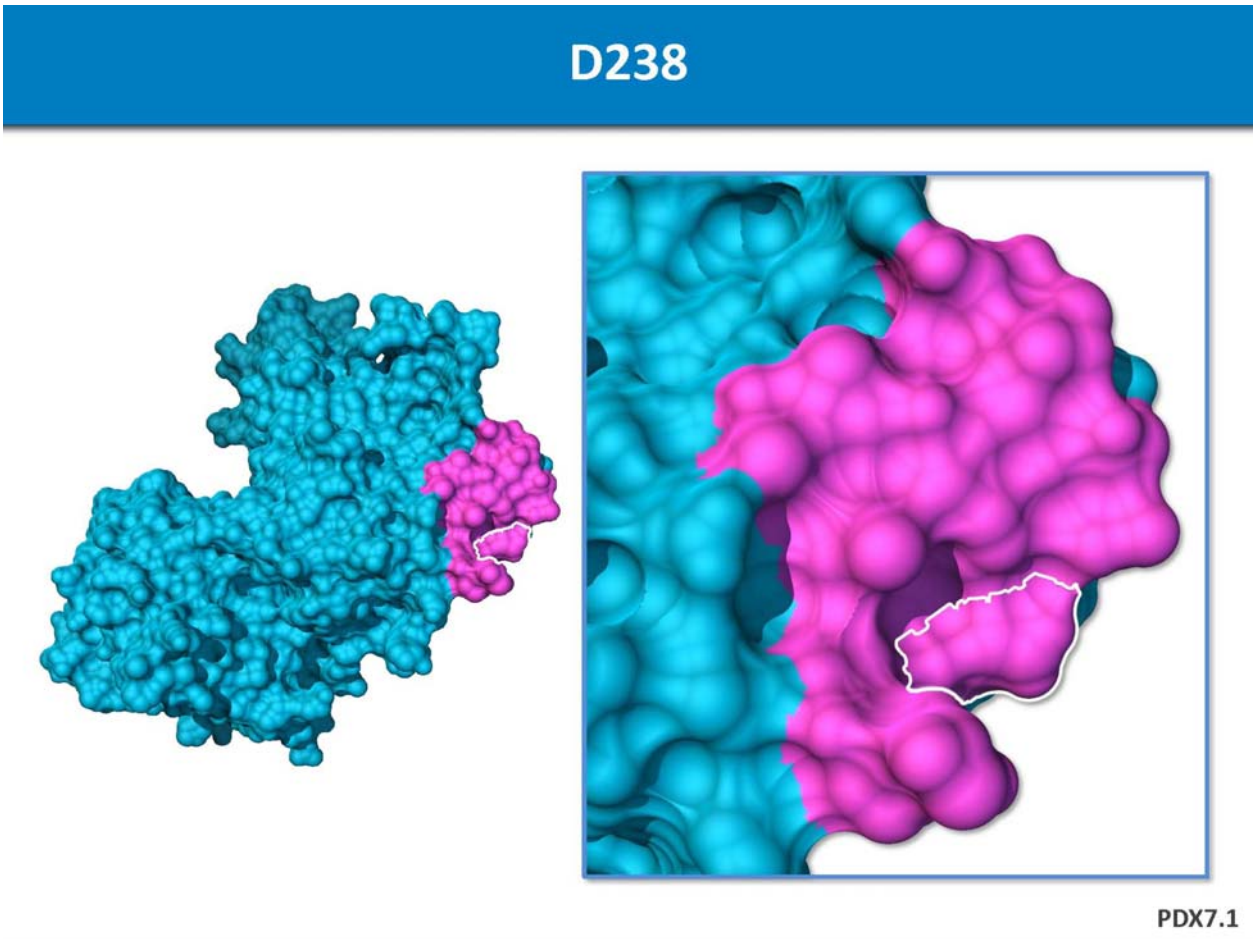


Ex.C,242:22-244:16; Ex.NN¶43-44.

Antibodies are complex proteins that have a characteristic "Y" shaped structure composed of well-defined regions. Ex.C,242:18,371:12-15; Ex.E,617:22-620:19; Ex.F,930:12-931:4. In the graphic below, the yellow portion is the structure that is consistent across all monoclonal antibodies. The portions at the tips of the arms (magenta) confer the specificity of the antibody to a particular target molecule:



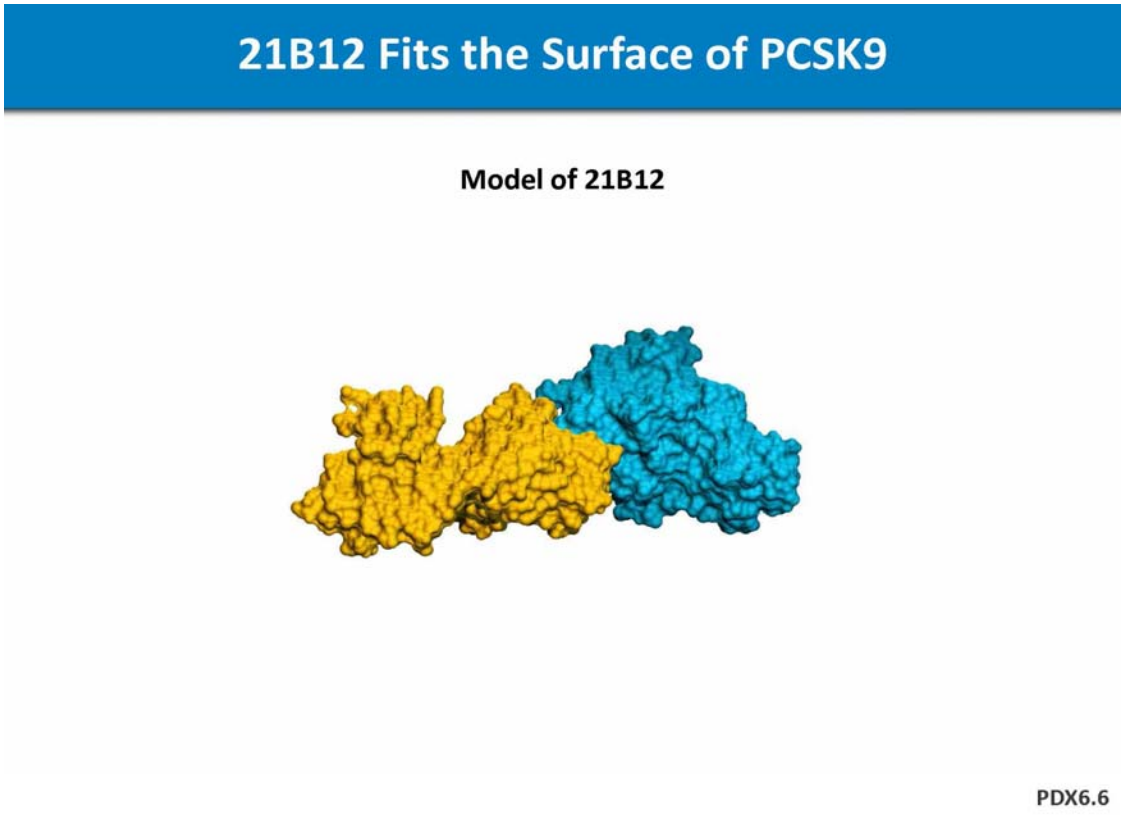
The patent claims-in-suit define monoclonal antibodies that bind to specific locations on PCSK9 (the "sweet spot") and block the interaction of PCSK9 with LDLR. Ex.A,427-30; Ex.B,427-29. Claim 1 of the '165 patent lists the 15 residues on PCSK9 to which LDLR binds—shown in pink in the graphic below taken from the PCSK9 crystal structure (with one of the residues, D238, outlined):



Ex.E,568:13-569:20.

The patents share a common specification and contain more than 300 pages of detailed descriptions of how to make, use and characterize the claimed antibodies. The patent examples disclose production of hundreds of antibodies and detailed analyses—binding, blocking, binning, and amino acid sequencing—for over two dozen antibodies. Ex.A,Figs.2,3,13,15,77:21-81,88:30-90:4,97:49-98:32; Ex.C,266:11-271:5; Ex.E,691:3-22,743:20-746:7; Ex.F,923:7-930:22.

The patents further provide detailed crystal structure data for two antibodies (21B12 and 31H4) bound to PCSK9 and of LDLR bound to PCSK9. That data define the binding sites on PCSK9 down to atomic level. Ex.A,99:56-108:60,Tables35.1-35.4; Ex.C,283:2-292:8; Ex.E,579:1-11, 676:2-677:6; Ex.F,803:11-818:17. One of these two antibodies, 21B12, shown below binding to the "sweet spot" on PCSK9, became Amgen's Repatha product:



Ex.F,906:22-908:24.

As attested by Amgen's experts at trial, the experiments in the patent were "well-conceived," "cleverly designed," Ex.E,770:17-19, and "an impressive piece of scientific work," Ex.F,897:14-15.

2. Substantial Evidence Supports The Jury's Verdict.

Whether a patent's written description "reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date" is a question of fact, and its application "will necessarily vary depending on the context," including "the state of the art from which [the patented advance] emerges." *Ariad Pharms. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). This Court has declined to "set out any bright-line rules governing, for example, the number of species that must be disclosed to describe a genus claim, as this number … changes with progress in a field." *Id.*

The district court correctly instructed the jury that the inventors must show possession of the invention. Although there are no limitations on how to demonstrate written description, it is adequate if it discloses: (i) a representative number of species of the claimed antibodies; (ii) common structural features, or (iii) "a newly-

characterized antigen" if the production of antibodies against such an antigen was conventional or routine in light of the skill in the art. Ex.G,23-25.

Amgen only had to prevail on *one* of those tests. *See AbbVie Deutschland GmbH v. Janssen Biotech*, 759 F.3d 1285, 1299 (Fed. Cir. 2014). The evidence supports the verdict under *all* of them. The court found that Amgen's experts "provided more than conclusory testimony in order to explain their respective conclusions to the jury. The jury credited such testimony over that of defendants' experts. … Viewing the record in the light most favorable to plaintiffs, substantial evidence supports the jury's verdict." Ex.H,26.

As the court found, Amgen's patent disclosure describes hundreds of antibodies that bind to PCSK9 and block the interaction of PCSK9 with LDLR "strongly." Ex.H,4; Ex.A,79:50-80:37. Of these, 85 antibodies were identified that blocked the interaction greater than 90%. *Id.* A subset were selected for sequencing and further characterization including binning assays to group the antibodies by where they bind on PCSK9. Ex.H,5; Ex.A,97:49-98:32, Figs.2,3,13,15. As the court explained, antibodies that were assigned to the same "bin"

would share the "same or overlapping epitopes." Ex.H,n.4; Ex.A,63:60-64:2,89:29-33. Two antibodies, 21B12 (which became Repatha) and 31H4 were representative of two epitope bins and were examined further using X-ray crystallography to determine their precise binding sites on PCSK9. Ex.H,5; Ex.A,88:30-89:37,100:30-108:60,Tables 35.1,35.3.

Amgen's expert Dr. Petsko explained that "the 15 residues that constitute the binding region are covered 'virtually perfectly' … by 21B12 and 31H4," Ex.H,18; Ex.F,806:15-20, and that these two antibodies provide "all the information needed to 'define the part of PCSK9 where the antibodies need to bind in order to block.'" Ex.H,19; Ex.F, 806:22-807:3,811:2-20. The court noted that Dr. Petsko used the binning and blocking data in the patent to conclude that the two dozen antibodies that co-bin with 21B12 or 31H4 "more likely than not" meet the limitations of the claims. Ex.H,20; Ex.F,798:6-802:25,819:5-22. The court cited to Dr. Jackson's testimony that, by using the crystal structures for 21B12 and 31H4 together with the binning data, the inventors "knew that the other antibodies were binding" in the claimed region. Ex.H,21; Ex.C,291:21-25. As described in the patents, these

additional antibodies were sequenced and shown to be quite diverse: they derive from seven different families, and have diverse sequences and highly varied structures. Ex.H,19,21; Ex.C,266:11-267:15; Ex.E,691:3-22,743:19-746:7; Ex.F,923:7-930:22.

Defendants try to wish away this disclosure and evidence by repeatedly arguing the patent discloses "only two, only two." But the jury heard compelling evidence that the patent discloses at least two dozen representative species within the scope of the claims.

The court similarly described Amgen's evidence on structure-function correlation by citing to the testimony of Drs. Petsko and Rees that the patents describe the "structural characteristics" that the claimed antibodies share in order to carry out the function of binding to specific residues on PCSK9 and blocking the interaction of PCSK9 with LDLR. Ex.H,22-23. The specification provides a detailed, three-dimensional map of PCSK9's "sweet spot" and precisely describes its chemical composition. *See id.*; Ex.A,99:56-100:27,Table35.2; Ex.C,286:23-291:14; Ex.E,579:1-11,676:8-677:6. The claimed antibodies bind to the "sweet spot" because they have the structural complementarity that allows a spatial and chemical "fit" between the

molecules. Ex.H,22-23. Thus, the patent "provides a person of skill in the art the ability to visualize and recognize antibodies falling within the claims." Ex.H,22. Contrary to Defendants' position, the law and the technology do not limit the structural description of antibodies to just their amino acid sequences.

In fact, the newly characterized antigen test confirms this point—an adequate description of the structure of the target is legally sufficient to describe the antibodies that bind to that target. *Noelle v. Lederman*, 355 F.3d 1343, 1349 (Fed. Cir. 2004). As discussed above, the patents were the first to disclose and characterize the specific claimed binding region on PCSK9. They also provide a detailed roadmap that a person skilled in the art could use to generate many more antibodies within the claim scope using routine and well established methods. Ex.H,23.

Although Defendants criticize the jury instruction on the "newly characterized antigen" test, that instruction came right out of this Court's decisions. *See Centocor Ortho Biotech v. Abbott Labs.*, 636 F.3d 1341, 1352 (Fed. Cir. 2011). And far from being *dicta*, this Court expressly "adopted" that test from the PTO's examination guidelines,

Noelle, 355 F.3d at 1349, after being "persuaded by the Guidelines on this point," *Enzo Biochem v. Gen-Probe*, 323 F.3d 956, 964 (Fed. Cir. 2002). Nor must the newly characterized antigen be a complete protein, as opposed to part of one, as Defendants argue. The PTO has expressly rejected that position, *Ex Parte Supuran*, 2011 WL 1661465, at *2-3 (B.P.A.I. Apr. 28, 2011); *Ex Parte Xia*, 2009 WL 220277, at *2,*5 (B.P.A.I. Jan. 28, 2009), and there is no reason the rule would turn on that consideration. *See generally Enzo*, 323 F.3d at 964.

Amgen disclosed more than sufficient information from which the jury could conclude that Amgen satisfied the written description requirement.

3. The District Court Did Not Abuse Its Discretion In Excluding Irrelevant And Cumulative Evidence.

Defendants attack the exclusion of post-priority-date evidence concerning Praluent and Amgen's next-generation research and development efforts. Such post-priority-date evidence is irrelevant because the adequacy of written description is determined as of the filing date. *Ariad*, 598 F.3d at 1355; *In re Koller*, 613 F.2d 819, 825 (C.C.P.A. 1980).

This Court did not reject this longstanding precedent in *AbbVie*. *See* 759 F.3d at 1302-03. That decision did not even consider the admissibility of post-priority-date evidence; instead, it upheld a jury verdict based on the record evidence.[1]

Once Defendants stipulated to infringement, the court found Praluent had no relevance, and it would have been confusing to the jury for Defendants to argue that the patents did not specifically describe Praluent. Ex.C,218:12-14. A patentee is not required to describe every specific embodiment within the scope of the claims. "The law does not require the impossible. Hence, it does not require that an applicant describe in his specification every conceivable and possible future embodiment of his invention." *SRI Int'l v. Matsushita Elec. Corp. of Am.*, 775 F.2d 1107, 1121 (Fed. Cir. 1985) (en banc); *see Cordis v. Medtronic AVE*, 339 F.3d 1352, 1365 (Fed. Cir. 2003) (applying same statement and upholding written description).

Moreover, Defendants ignore the second, discretionary basis for the district court's exclusion of post-priority-date evidence: that it would

[1] In *AbbVie*, the patentee relied only on the representative-species test, and all of the disclosed antibodies had highly similar structures—not the facts here. *See* 759 F.3d at 1291, 1293, 1299.

have been "at best cumulative," as Defendants had the ability to, and did in fact, make all of their arguments attacking written description without referring to Praluent. Ex.C,218:18-19. The court's ruling cut both ways and precluded Amgen from presenting evidence of later characterization of antibodies actually disclosed in the patent to show the very features that Defendants claimed were "missing," *e.g.*, a "middle binder." Ex.I; Ex.J,4-5. The court's evenhanded trial-management decision was not a "clear abuse of discretion." *Joy Mfg. v. Sola Basic Indus.*, 697 F.2d 104, 111 (3d Cir. 1982).

4. JMOL Was Proper On Obviousness.

The district court correctly granted JMOL on obviousness as Defendants failed to establish that two third-party patent applications filed *after* Amgen's priority date were entitled to the benefit of earlier provisional filings. The provisional filings themselves are not prior art because they were unpublished. *See* 35 U.S.C. §102(a),(b).

The court correctly applied the statute in requiring Defendants to show that the provisionals provided written descriptive support for a claim in the subsequent applications in order to establish the applications as prior art. An application is entitled to the priority date

of a provisional only if the "invention [was] *disclosed in the manner provided by section 112(a) … in a provisional application*." 35 U.S.C. § 119(e)(1) (emphasis added). This Court has repeatedly construed that statutory language to require that the provisional filing must provide written description for at least one claim in the subsequent application. *Dynamic Drinkware v. Nat'l Graphics*, 800 F.3d 1375, 1378 (Fed. Cir. 2015); *New Railhead Mfg. v. Vermeer Mfg.*, 298 F.3d 1290, 1294 (Fed. Cir. 2002).

Defendants' argument that cases like *Drinkware* apply only to issued patents and not to applications is undone by the express language of the statute: "[a]n application for patent," 35 U.S.C. §119(e)(1). In any case, there is no reason to treat applications and issued patents differently for this purpose. *Ariosa Diagnostics v. Illumina*, 2016 WL 354412 (PTAB Jan 7, 2016).

Defendants' characterization of the court's decision as reactionary "following one-page briefing," is simply wrong as the court ruled on this issue before trial and gave Defendants multiple opportunities to supplement their expert reports to provide the needed support. *E.g.*, Ex.L,4. The parties presented oral argument at the pretrial conference

for 13 pages of transcript. Ex.K,52-64. After issuing a very reasoned opinion, the court delayed the start of trial to give Defendants one last chance. Ex.L; *id.* at 4. When Defendants failed to provide any meaningful evidence of 112 support, the court granted JMOL.

5. The District Court Did Not Abuse Its Discretion In Granting A Permanent Injunction.

In analyzing the four injunction factors, the court found that Amgen had suffered irreparable harm due to Defendants' direct competition in a two-player market and that money damages were speculative and insufficient to compensate Amgen for its loss of exclusivity. Ex.M,5. The court found that the balance of hardships was neutral, and that the public has an interest in having a choice of drugs available. Based on the court's findings, it would have been an abuse of discretion *not* to grant an injunction.

Defendants repeatedly attack the court's opinion as providing only a "perfunctory analysis and wholly unreasoned conclusion." But, the court found that Amgen had shown irreparable harm by the "traditional evidence of loss of market share and momentum." Ex.M,5. Defendants have deprived Amgen of market share and enabled insurers to pit the

parties against each other to extract unprecedented concessions. Ex.D,144:20-145:8,147:16-148:7,150:2-11; Ex.OO¶¶10-11; Ex.PP¶5. As this Court has observed, "[c]ompetitors change the marketplace," causing irreparable injuries. *Polymer Techs. v. Bridwell*, 103 F.3d 970, 975 (Fed. Cir. 1996); *accord Douglas Dynamics v. Buyers Prods.*, 717 F.3d 1336, 1344 (Fed. Cir. 2013) .

Repatha and Praluent "are the only therapeutics in the PCSK9 inhibitor market, making the parties head-to-head competitors in a targeted and developing market." Ex.M,4. Further, as the court explained, permanent injunctions are "frequently" granted when "the market for the patented technology is volatile or still developing." *Id.*

The court found that Amgen's reputation had been harmed by Defendants' infringement. Ex.M,5. Especially where, as here, a patentee has a history of not licensing its patents to maintain market exclusivity, Ex.D,67:21-68:14, the right to exclude is an "intangible asset that is part of the company's reputation." *Douglas*, 717 F.3d at 1345. The court found that "[m]onetary damages will not suffice under the present circumstances, as plaintiffs intend to use their patent to

maintain market exclusivity," and found this factor weighed in favor of Amgen. Ex.M,5.

The court found the "balance of hardships" to be neutral. Under settled law, Defendants' investment in an infringing product does not shield them from an injunction. "One who elects to build a business on a product found to infringe cannot be heard to complain if an injunction against continuing infringement destroys the business so elected." *Robert Bosch v. Pylon Mfg.*, 659 F.3d 1142, 1156 (Fed. Cir. 2011).

Defendants repeatedly assert that the court's finding of public interest favoring a "choice of drugs" should compel no injunction. But the court did not accept Defendants' argument that a "low dose" is better, expressly stating that it "will not substitute its judgment for that of the FDA." Ex.M-6. Rather, the court stated the general principle that the "public generally is better served by having a choice of available treatments." *Id.* This "choice" argument, however, could be argued in every case where a competitor brings a product to market, and the court would have abused its discretion by *denying* an injunction based on public "choice." *See WBIP v. Kohler*, 829 F.3d 1317, 1343 (Fed. Cir. 2016). "[H]aving more manufacturers of a life-saving good in the

market" is not a sufficient basis for denying injunctive relief. *Id.* See also Ex.-PP¶¶26-30.

Defendants argue that the "public interest" factor should trump the other equitable factors. But, the court did not find that the public interest in "choice" outweighed the other injunction factors. The decision to grant injunctive relief has always involved "weighing relevant factors," as the court clearly did here, under the familiar four-part test. *Innogenetics v. Abbott Labs.*, 512 F.3d 1363, 1379 (Fed. Cir. 2008). "No one factor, taken individually, is necessarily dispositive." *FMC v. United States*, 3 F.3d 424, 427 (Fed. Cir. 1993). *eBay v. MercExchange*, confirmed that the traditional balancing test applies in every case, and that there are no categorical rules governing a court's exercise of its discretion. 547 U.S. 388, 391-93 (2006).

The public interest is served by giving meaning to a patent's exclusionary right. Evidence at the hearing demonstrated that developing new therapeutic products is a costly endeavor—here, Amgen spent over $2 billion in bringing Repatha to market. Ex.D,60:12-19. Amgen made that investment relying on the strong intellectual property protection around Repatha. Ex.D,60:1-11,65:2-19; *see also*

Ex.PP¶9.

If patents are not enforced by injunctions, the business model of an innovative biotech or pharmaceutical company collapses. Ex.D, 57:25-59:1,229:5-20; Ex.PP¶¶8-9,22,25. No company will expend the resources necessary to bring breakthrough products to market only to have others develop similar products and compete in the marketplace. *Id.* The public will be disserved by not having access to new treatments for the health challenges and diseases of our day. *Bio-Tech. Gen. v. Genentech*, 80 F.3d 1553, 1566 (Fed. Cir. 1996). Indeed, there is a "significant public interest in encouraging investment in drug development and protecting the exclusionary rights conveyed in valid pharmaceutical patents." *Sanofi-Synthelabo v. Apotex*, 470 F.3d 1368, 1384 (Fed. Cir. 2006).

Courts have routinely granted injunctions in pharmaceutical patent cases upon a finding of liability. *See*, *id.*; *Amgen v. F. Hoffman-La Roche*, 581 F. Supp. 2d 160, 226-27 (D. Mass. 2008), *aff'd in part, rev'd in part on other grounds*, 580 F.3d 1340 (Fed. Cir. 2009). Defendants cite no counter-examples, no cases of compulsory licensing as they suggest, only a case affirming the denial of a *preliminary*

injunction against a medical device, *Cordis Corp. v. Boston Scientific Corp.*, 99 F. App'x 928 (Fed. Cir. 2004), and another case in which a plaintiff evidently chose not to request a permanent injunction.

B. Amgen's Irreparable Harm Continues While Defendants' Proposed Harms Are Self-Inflicted.

Defendants' infringement and direct competition in this two-supplier market continue to cause Amgen to suffer reputational harm and lost sales. Ex.PP,¶¶4-12; Ex.OO¶¶10-13,15-16.

Nor would a stay preserve the status quo. Every day that passes without enforcing the injunction lets Defendants further solidify their position in the market and expand their patient and doctor bases, making it harder for Amgen to capitalize on its exclusive rights once the injunction goes into effect. Ex.OO,¶¶8-13; Ex.PP,¶¶4-6. Any further delay in injunctive relief would impact price and contract negotiations with payers for 2018-2019. Ex.OO,¶13. Staying the injunction exacerbates and further extends Amgen's irreparable harm.

Defendants' alleged harms if a stay is denied are all functions of their decision to launch an admittedly infringing product at risk. Ex.PP¶¶13-17. Defendants knew as early as 2009 that there would be "patent issues" with pursuing any antibody that bound to the same

epitope on PCSK9 as Amgen's antibodies. Ex.D,191:11-193:25. Defendants' experimental evidence confirmed that Praluent binds to the same "sweet spot." *Id.* At that point, the responsible action was to stop. Several other companies dropped their PCSK9 antibody programs in view of Amgen's patents. Ex.Q,525:17-526:3. Amgen's CEO Robert Bradway gave a real-world example of a different Amgen program that was halted due to a prior-filed Regeneron patent application. *Id.*

Instead, Defendants rushed forward. After realizing they were behind Amgen in filing with the FDA, *and after the filing of this lawsuit*, Defendants used a priority-review voucher so they could jump the queue and get FDA approval before Amgen. Ex.M,2. Rather than wait eight months for the results of the jury trial, Defendants built out their sales and marketing capacity, launched at-risk and flooded the market with free Praluent to quickly gain market share. Ex.OO¶10; Ex.Q,313:1-316:20. Such irresponsible behavior cannot create "harms" that justify avoiding the injunction.

For example, Defendants argue that they would lay off employees, who they describe as "the heart of their businesses," during this appeal. Whether to let their "heart" go during an expedited appeal is, of course,

Defendants' decision. But such self-inflicted harms cannot weigh in their favor. *See Merial v. Cipla*, 681 F.3d 1283, 1306 (Fed. Cir. 2012).

Defendants' and their amici speculate that, absent a stay, their ongoing clinical trials could be disrupted. Clinical trials are exempt from infringement under 35 U.S.C. 271(e), and patients in such clinical trials never know if the product will ever reach the market. Ex.NN,¶¶56-60.

Defendants point the finger at Amgen, suggesting that it has brought any harm on itself by "deliberately cho[osing] *not* to seek a preliminary injunction." The district court expressed a strong preference for an expedited trial schedule instead of a preliminary injunction and Defendants agreed. Ex.N,12:14-13:11,16:25-17:4; Ex.O,20n.34; Ex.K,6:3-11. There is no reason to hold that decision, or the nine months that elapsed between trial and the district court's entry of the injunction, against Amgen. *See Mytee Prods. v. Harris Research*, 439 F. App'x 882, 888 (Fed. Cir. 2011).

Defendants' actions in continuing to develop Praluent and launching at risk in the face of Amgen's patents were irresponsible and should not be rewarded with a stay.

C. No Patient Will Go Untreated.

Defendants erroneously contend that "many Praluent patients will be left with *no* realistic option" because their "half-dose" option is purportedly the only "medically sound" treatment available. The FDA found that Repatha can safely and effectively treat all patients for whom Praluent is approved. Ex.NN¶14. Likewise, payers treat Repatha and Praluent as "therapeutically equivalent." Ex.PP¶¶26-30. Defendants ask this Court to substitute its judgment on the safety of Amgen's Repatha for that of the FDA. The district court refused to do so, and so should this Court because there is no evidence to suggest that Amgen's Repatha is unsafe. Ex.NN¶¶14,23,34,50.

Defendants proffered no objective evidence at trial of any safety risk from "very low" LDL-C levels, *i.e.,* below 25 mg/dL, and present none now to support their inflammatory speculations. Indeed, Dr. Eckel admitted that he knew of no such evidence. Ex.Q,435:21-23,436:10-19. In their post-trial injunction briefing, Defendants again admitted there was "no evidence" of such a safety risk. Ex.P,13. In fact, data submitted to the FDA from the clinical trials conducted by both parties show just the opposite—that many patients' LDL-C levels

went below 25 mg/dL, or even 15 mg/dL, with no safety signal. Ex.NN¶¶22-23,25. The FDA rejected Defendants' attempts to claim a difference in efficacy between their "half-dose" and "full-dose" Praluent—exactly the same arguments Defendants posit here. Ex.NN¶¶37-40,48-49.

More data published since the trial confirms the benefits and safety of achieving "very low" levels of LDL-C. Amgen's widely-heralded GLAGOV study, published in JAMA in November 2016, showed that 80% of patients achieving "very low" levels of LDL-C had a reduction in plaque build-up in their arteries with no safety concerns. Ex.NN¶35. Attempting to ride on Amgen's coattails, Defendants and Dr. Eckel have recently published data showing that use of "full-dose" Praluent can achieve "very low" LDL-C levels with no safety signals being observed. Ex.NN¶¶30-34.

Defendants wrongly assert that the transition from Praluent to Repatha will take months, be "complex and costly," and "leave patients untreated in the interim." Any patient not currently on Repatha either has access to it or Amgen can facilitate such access quickly and easily. Ex.OO¶21; Ex.PP¶19. The medical community has experience with

transferring patients from one drug to another, and all patients can be successfully transitioned to Repatha without interruption or difficulty. Ex.OO ¶¶18-19, 22-29, Ex. PP ¶¶18-21; see also Ex.NN, ¶¶19-20. Amgen has identified and can quickly contact those physicians who do not have experience prescribing Repatha. Ex.OO¶¶18-19. Payers having "exclusive" agreements for Praluent already use Repatha for approximately 30% of their patients, *id.*¶21, and several of these payers have contacted Amgen about putting new agreements in place. *Id.*¶29; Ex.PP¶19. There are no barriers to physicians and patients getting access to Repatha immediately when the injunction becomes effective.

It is undisputed that Amgen has ample manufacturing and patient/physician support capacity to serve the entire market today and going forward. Ex.D,67:13-20,170:24-171:19,134:17-135:25; Ex.OO,¶17, 19; Ex.PP,¶23. Defendants' allegation that Repatha could be recalled in the future is sheer speculation and does nothing to contravene the actual, undisputed evidence of Amgen's capabilities to supply the entire market once the injunction take effect. *See* Ex. PP ¶¶22-23; see also Ex.NN,¶51.

CONCLUSION

This Court should deny the motion for a stay pending appeal.

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

I certify that this paper complies with the type-volume limitation of Fed. Cir. R. 8(b)(1) because it contains 5,197 words inclusive of 109 words in the figures, excluding the parts of the brief exempted by Fed. R. App. P. 32(f). This paper complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the typestyle requirements of Fed. R. App. P. 32(a)(6) because it has been prepared in 14-point, proportionally spaced typeface using Microsoft Word.

January 27, 2017

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CERTIFICATE OF SERVICE

I certify that on January 27, 2017, I caused the foregoing to be filed with the Court electronically using the CM/ECF system, which will send a notification to all counsel of record.

January 27, 2017

/s/ Daryl L. Joseffer
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